DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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Rec'd 11/19/08

Alan R. Bennett
Ropes & Gray, LLP
One Metro Center
700 12th Street, NW
Suite 900
Washington, DC 20005-3948

Re: Docket No. FDA-2006-P-0073

Dear Mr. Bennett:

This letter responds to your citizen petition dated June 9, 2006, submitted on behalf of AstraZeneca LP (Petition).[1] The Petition requests that the Food and Drug Administration (FDA) publish a draft guidance on the demonstration of bioequivalence for locally acting oral inhalation suspension products and allow a period of public comment on the guidance before approving any abbreviated new drug application (ANDA) for a generic version[2] of Pulmicort Respules (budesonide inhalation suspension or BIS). The Petition also requests that FDA:

1. determine that labeling for a generic budesonide inhalation suspension product that omits once-daily dosing language would be legally impermissible
2. require any ANDA applicant for a BIS product to conduct a clinical trial program to demonstrate bioequivalence to Pulmicort Respules
3. examine whether it would be more appropriate to consider only applications submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)[3] rather than ANDAs for approval of a generic BIS product, and
4. require any generic BIS product to meet certain product quality standards.

In addition, you submitted a supplement dated September 18, 2008, (the September Supplement) regarding the July 23, 2008, meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology on Bioequivalence of Inhalation Drug Products and the FDA's July 28, 2008, letter responding to a citizen petition involving Camptosar (irinotecan hydrochloride).[4] You also submitted another supplement dated October 9, 2008 (the October Supplement) regarding statements apparently made by IVAX Pharmaceuticals, Inc., concerning the proposed labeling for its budesonide inhalation suspension. We have carefully reviewed the Petition, the

[1] This citizen petition was originally assigned docket number 2006P-0242/CP1. The number was changed to FDA-2006-P-0073 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] For purposes of this response, the term *generic version* or *generic drug* refers to new drug products for which approval is sought in an ANDA submitted under section 505(j) of the Act.

[3] 21 U.S.C. 355(b)(2).

[4] Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Ernest Lengle, Ph.D., Executive Director, Regulatory Affairs, Watson Laboratories (July 28, 2008) (Docket No. 2008-P-0069).

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September and October Supplements, and comments filed in the docket. For the reasons described below, the Petition is granted in part and denied in part.[5]

I. BACKGROUND

A. Pulmicort Respules

1. NDA Approval

AstraZeneca is the new drug application (NDA) holder for Pulmicort Respules (budesonide inhalation suspension or BIS) (NDA 20-929), which has been approved in 0.25 mg/2 ml, 0.5 mg/2 ml, and 1 mg/2 mL strengths. NDA 20-929 was approved on August 8, 2000. BIS is an inhaled corticosteroid and is an inhalation suspension that consists of solid particles of budesonide suspended in an aqueous fluid. BIS is supplied in sterile single-use ampules to be used with a nebulizer. The nebulizer generates droplets from the suspension that the patient then inhales while breathing normally through a face mask or mouthpiece. The nebulizer is commercially available separately from Pulmicort Respules.

Pulmicort Respules is indicated for the maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age. The approved labeling for Pulmicort Respules includes in the DOSAGE AND ADMINISTRATION section a table with the recommended starting dose and highest recommended dose of budesonide based on prior asthma therapy. For patients previously on bronchodilator, inhaled corticosteroid, or oral corticosteroid therapy, the highest recommended dose of BIS is 0.5 mg total daily dose, 1.0 mg total daily dose, and 1.0 mg total daily dose, respectively. The Pulmicort Respules labeling stipulates that the recommended starting dose may be administered as either the total daily dose once daily or in divided doses twice daily. The Pulmicort Respules labeling also includes a statement regarding consideration of an alternative once-daily dose for "symptomatic children not responding to nonsteroidal therapy" (corticosteroid naïve patients). The labeling also includes a statement stipulating that it is desirable to downward-titrate to the lowest effective dose once asthma stability has been achieved.

2. Patents Listed for Pulmicort Respules

In FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (which is generally known as the "Orange Book"), Pulmicort Respules is listed with method of use patents 6,598,603 and 6,899,099 for "Once daily treatment of asthma with nebulized budesonide." Both

[5] Today we are approving one ANDA for a generic version of Pulmicort Respules in 0.25 milligram (mg)/2 milliliter (ml) and 0.5 mg/2 ml strengths.

patents expire on December 23, 2018, and pediatric exclusivity associated with these patents expires on June 23, 2019.

The Petition states that in September 2005, AstraZeneca received notice that IVAX Pharmaceuticals, Inc. (IVAX) had submitted an ANDA to obtain approval for a generic BIS drug product (Petition at 2). The Petition states that in IVAX's notice letter regarding AstraZeneca's method of use patents directed to once-daily dosing of nebulized budesonide, IVAX informed AstraZeneca that it is proposing to eliminate references to once-daily dosing from the labeling of its proposed generic BIS drug product (Petition at 4).

B. Dosage Forms for Inhaled Drug Products

There are several different dosage forms that can be used to deliver inhaled drug products to the lungs. These dosage forms include:

- Inhalation solutions
- Inhalation suspensions
- Metered dose inhalers (MDI)
- Dry powder inhalers (DPI)

Inhalation solutions and inhalation suspensions are distinguished by the state of the active ingredient in their aqueous fluid. The active ingredient in inhalation solutions is dissolved in the fluid. In contrast, the active ingredient in inhalation suspensions remains undissolved in the fluid. Both inhalation solutions and suspensions are used with nebulizers that are commercially available separately from the inhalation solution or suspension.

MDIs and DPIs are drug products that produce dispersed particles of active ingredient for inhalation. MDIs contain active ingredient(s) dissolved or suspended in a propellant, a mixture of propellants, or a mixture of solvent(s), propellant(s), and/or other excipients in compact pressurized aerosol dispensers.

DPIs contain active ingredient(s) alone or with an excipient(s) and no propellent or solvent. Designs include pre-metered and device-metered DPIs, both of which can be driven by patient inspiration alone or with power-assistance of some type. Pre-metered DPIs contain previously measured doses or dose fractions in some type of units (e.g., single or multiple presentations in blisters, capsules, or other cavities) that are subsequently inserted into the device during manufacture or by the patient before use. Device-metered DPIs typically have an internal reservoir containing sufficient formulation for multiple doses which are metered by the device itself during actuation by the patient.

Each of these dosage forms have unique characteristics that should be considered when determining appropriate methods for demonstrating bioequivalence of the generic drug product. This response focuses on the bioequivalence and other regulatory requirements for generic versions of BIS (an inhalation suspension) only.

C. Legal Framework

Before addressing the arguments you make in the Petition and Supplements, it is useful to summarize the statutory and regulatory provisions related to (1) ANDA approval and demonstrating bioequivalence, (2) ANDA approval with respect to listed patents and marketing exclusivity, and (3) ANDA approval for a drug product whose labeling omits an indication that is protected by a patent.

1. Statutory and Regulatory Basis for ANDA Approval and Demonstrating Bioequivalence

a. Summary of Basis for ANDA Approval

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Act (21 U.S.C. 355(j)), which established the current ANDA approval process. To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the RLD[6] is safe and effective. Under the Hatch-Waxman Amendments, to rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its generic drug is bioequivalent to the RLD.[7] In addition, a drug product described in an ANDA generally must contain the same active ingredient,[8] conditions of use,[9] route of administration, dosage form, strength,[10] and (with

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[6] A reference listed drug or RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs are identified in the Orange Book.

[7] See, e.g., section 505(j)(2)(A)(iv) of the Act (requiring "information to show that the new drug is bioequivalent to the listed drug referred to in clause (i) [i.e., listed drug]..."); 21 CFR 314.3 (defining *reference listed drug*); 21 CFR 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the reference listed drug upon which the applicant relies); 21 CFR 314.127(a)(6)(i)(providing that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the ANDA); and the Orange Book, Introduction at p. x (defining *reference listed drug*).

[8] See, e.g., 21 CFR 314.94(a)(5).

[9] See, e.g., 21 CFR 314.94(a)(4).

[10] See, e.g., 21 CFR 314.94(a)(6).

certain permissible differences) labeling[11] as the RLD, unless a petition for certain changes is approved by the Secretary[12] (section 505(j)(2)(A), (j)(2)(C), and (j)(4) of the Act). An ANDA applicant also must demonstrate that its generic drug product meets approval requirements relating to the chemistry, manufacturing, and controls for the drug product. Under section 505(j)(4)(A) of the Act, an ANDA must be approved by FDA unless it finds, among other things, that "the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity." Drug products that meet the approval requirements under section 505(j) and are both bioequivalent and pharmaceutically equivalent[13] to the RLD are considered by FDA to be therapeutically equivalent to the RLD. Therapeutically equivalent drugs generally may be substituted for each other with the expectation that the substituted product will produce the same clinical effect and safety profile when used according to the labeling.[14]

b. Bioequivalence

The statute, regulations, and case law give FDA considerable flexibility in determining how ANDA applicants can meet the requirement referenced above for establishing bioequivalence. Section 505(j)(8)(B)(i) of the Act states that a generic drug is bioequivalent to the RLD if the following conditions exist:

> . . . the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . . .[15]

However, section 505(j)(8)(C) of the Act recognizes that different approaches may apply to locally acting or nonsystemically absorbed drug products. It states the following:

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[11] See, e.g., 21 CFR 314.94(a)(8).

[12] An applicant may submit an ANDA for a drug that has a different active ingredient, route of administration, dosage form, or strength from the RLD if the applicant has submitted a petition to the Agency (known as a *suitability petition*) requesting permission to file such an application and has received the Agency's approval (see section 505(j)(2)(C) of the Act and 21 CFR 314.93).

[13] Pharmaceutically equivalent drug products have the identical dosage forms that contain identical amounts of the identical active drug ingredient and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. They do not necessarily contain the same inactive ingredients and may also differ in characteristics such as shape, scoring, release mechanism, and, within certain limits, labeling (see 21 CFR 320.1 and the Orange Book, Introduction at p. vii).

[14] See the Orange Book, Introduction at p. vii.

[15] See also 21 CFR 320.1(e) and 320.23(b).

> For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

FDA's regulations similarly reflect the flexibility that FDA has in choosing the appropriate methods to establish bioequivalence for particular drug products. Under the regulations, bioequivalence may be demonstrated by several in vivo and/or in vitro methods. The regulations provide the following:

> FDA may require in vivo ***or in vitro testing, or both***, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products [emphasis added]. . . . The selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section. The method used must be capable of measuring bioavailability or establishing bioequivalence, as appropriate, for the product being tested.[16]

FDA regulations at 21 CFR 320.24 describe these methods in descending order of accuracy, sensitivity, and reproducibility. They generally include (1) in vivo pharmacokinetic studies, (2) in vivo pharmacodynamic effect studies, (3) clinical endpoint studies, and (4) in vitro studies.[17] In addition, consistent with section 505(j)(8)(C) of the Act, § 320.24(b)(6) of the regulations states that FDA has the flexibility to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence."

Ultimately, under the statute and regulations, the choice of study design is based on the ability of the design to compare the drug delivered by the two products at the particular site of action of the drug. The courts that have considered FDA's bioequivalence methodologies have also consistently upheld FDA's scientific discretion in this regard (see, e.g., *Schering Corp. v. FDA*, 51 F.3d 390 at 397-400 (3rd Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994); *Bristol Myers Squibb Co. v. Shalala*, 923 F. Supp. 212 (D.D.C. 1996)). As the *Bristol Myers Squibb* court noted, FDA has been given "the discretion to determine whether in vitro, or in vivo bioequivalence studies, or both, are required for the approval of generic drugs under the abbreviated application process" (*id.* at 217). Thus, bioequivalence for different types of drug products can be shown in different ways.

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[16] 21 CFR 320.24(a).

[17] 21 CFR 320.24.

2. ANDA Approval With Respect to Listed Patents and Marketing Exclusivity

The Act and FDA regulations require that an applicant seeking to market an innovator drug submit an NDA. NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug for the indication for which approval is sought. The Act and FDA regulations also require that an NDA applicant submit to FDA a list of patents claiming the approved drug substance, drug product, or approved method of using the drug product described in the NDA. Specifically, section 505(b)(1) of the Act requires NDA applicants to file as part of the NDA "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or *which claims a method of using such drug* and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug" (emphasis added).[18] FDA is required to publish patent information for drugs approved under section 505(c) and does so in the Orange Book (sections 505(b)(1), (c)(2), and (j)(7) of the Act and 21 CFR 314.53(e)).

As described in the previous section of this response, a drug product with an effective approval under section 505(c) is known as a *listed drug*,[19] and each ANDA applicant must identify the RLD on which it seeks to rely for approval. As described in more detail below, the timing of ANDA approval depends on, among other things, the intellectual property protections for the RLD that the ANDA references and whether the ANDA applicant challenges those protections (see section 505(b), (c), (j)(2)(A)(vii), and (j)(5)(B) of the Act).[20] In general, an ANDA may not obtain final approval until listed patents and marketing exclusivity have expired or until NDA holders and patent owners have had the opportunity to defend relevant patent rights in court.

Specifically, with respect to each patent submitted by the NDA applicant for the RLD and listed in the Orange Book, the ANDA applicant generally must submit to FDA one of four specified

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[18] Section 505(c)(2) of the Act imposes an additional patent submission requirement on holders of approved NDAs when those holders subsequently obtain new patent information that could not have been submitted with the NDA.

[19] Under 21 CFR 314.3(b), "*[l]isted drug* means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness." A listed drug is identified as having an effective approval in the Orange Book, which includes patent information for each approved drug (21 CFR 314.3(b) and 21 CFR 314.53(e)).

[20] Relevant intellectual property protections affecting the timing of ANDA approval include marketing exclusivity and listed patent protection for the listed drug. Because AstraZeneca currently has no marketing exclusivity for budesonide inhalation suspension, this response does not address the effect of marketing exclusivity on ANDA approval but focuses, instead, on relevant patent protection.

certifications under section 505(j)(2)(A)(vii) of the Act. The certification must state one of the following:

(I) that the required patent information relating to such patent has not been filed (Paragraph I certification);
(II) that such patent has expired (Paragraph II certification);
(III) that the patent will expire on a particular date (Paragraph III certification);
(IV) that such patent is invalid or will not be infringed by the drug for which approval is being sought (Paragraph IV certification).

The purpose of these certifications is "to give notice, if necessary, to the patent holder so that any legal disputes regarding the scope of the patent and the possibility of infringement can be resolved as quickly as possible" (*Torpharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 71 (D.D.C. 2003)).

If an applicant files a paragraph I or II certification, the patent in question will not delay ANDA approval. If an applicant files a paragraph III certification, the applicant agrees to wait until the relevant patent has expired before seeking full effective approval of its ANDA.

If, however, an applicant wishes to seek approval of its ANDA before a listed patent has expired by challenging the validity of a patent or claiming that a patent would not be infringed by the product proposed in the ANDA, the applicant must submit a paragraph IV certification to FDA. The applicant filing a paragraph IV certification must also provide a notice to the NDA holder and the patent owner stating that the application has been submitted and explaining the factual and legal bases for the applicant's opinion that the patent is invalid or not infringed (see section 505(j)(2)(B) of the Act).

The filing of a paragraph IV certification "for a drug claimed in a patent or the use of which is claimed in a patent" is an act of patent infringement (35 U.S.C. 271(e)(2)(A)). If the patent owner or NDA holder brings a patent infringement suit against the ANDA applicant within 45 days of the date it received notice of the paragraph IV certification, the approval of the ANDA will be stayed for 30 months from the date of such receipt by the patent owner and NDA holder, unless a court decision is reached earlier in the patent case or the patent court otherwise orders a longer or shorter period (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the Act). When the 30 months have expired, the patent ceases to be a barrier to final ANDA approval, even if the patent litigation is ongoing. Similarly, if the NDA holder and patent owner receive notice of a paragraph IV certification and decline to sue within 45 days of receipt of notice, the patent will not be a barrier to ANDA approval.

These four certifications are not the only manner in which an ANDA applicant may address all relevant patents. If a patent is listed only for a method of use and an ANDA applicant seeks to omit the method of use covered by the listed patent, the ANDA applicant may not file a paragraph I-IV certification for that patent. Instead, the applicant must submit a "section viii statement" acknowledging that a given method-of-use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval (see section 505(j)(2)(A)(viii) of the Act). Specifically, section 505(j)(2)(A)(viii) of the Act provides that "if with respect to the listed drug referred to in [section 505(j)(2)(A)(i)] information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the ANDA must contain] a statement that the method of use patent does not claim such a use." Such a statement requires the ANDA applicant to omit from its labeling information pertaining to the protected use (21 CFR 314.92(a)(1) and 314.94(a)(12)(iii)). If an ANDA applicant files a section viii statement, the patent claiming the protected method of use will not serve as a barrier to ANDA approval.[21]

FDA implementing regulations at 21 CFR 314.94(a)(12)(iii) describe the applicability of the section viii statement. Section 314.94(a)(12)(iii) states that:

> If patent information is submitted under section 505(b) or (c) of the [A]ct and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, [the ANDA applicant must submit] a statement explaining that the method of use patent does not claim any of the proposed indications.[22]

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[21] The Agency's interpretation of the plain language of the Act is further supported by Congressional intent as evidenced by the passage below:

> . . .The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved. For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication.

H.R. Rep. No. 857 (Part I), 98th Cong., 2d sess. 21.

[22] FDA regulations use the term *indications* to refer to information an ANDA applicant omits from its labeling in the context of submitting a statement that a protected use of a drug is not claimed in a listed patent (§ 314.94(a)(12)(iii)). However, the preambles for the proposed rule and final rule on patent and exclusivity provisions related to ANDA approval express no intent to distinguish between method of use and indication, using the terms interchangeably (see, e.g., 59 FR 50338 at 50347 (October 3, 1994)). Moreover, the preamble to the final rule emphasizes that an ANDA applicant does not have the option of choosing between a paragraph IV certification and a section viii statement; where the labeling does not include the indication, only the section viii statement is appropriate (id.). The preamble to the proposed rule states that where "the labeling for the applicant's proposed drug product does not include any indications that are covered by the use patent," the ANDA applicant would submit a section viii statement rather than a paragraph IV certification (54 FR 28872 at 28886 (July 10, 1989)).

Accordingly, FDA regulations also expressly recognize that by submitting a section viii statement, an ANDA applicant may omit from the proposed labeling a method of use protected by a listed patent and, therefore, need not seek approval for that use.[23]

The right to file a section viii statement and carve out from labeling method-of-use information protected by a patent has been upheld by the courts. Thus, in *Purepac Pharmaceutical Company v. Thompson*, 354 F.3d 877 (D.C. Cir. 2004), the D.C. Circuit stated that a "section viii statement indicates that a patent poses no bar to approval of an ANDA because the applicant seeks to market the drug for a use other than the one encompassed by the patent" (id. at 880). Similarly, in *Torpharm*, 260 F. Supp. 2d at 73, the D.C. District Court stated that a section viii statement "avers that the patent in question has been listed, but does not claim a use for which the applicant seeks FDA approval." These courts have upheld the Agency's interpretation that an ANDA applicant may choose not to seek approval for a method of use protected by a listed patent and, under those circumstances, that patent will not be a barrier to ANDA approval.

Thus, under the procedures established in the Hatch-Waxman Amendments, an ANDA will not be approved until all listed patents (1) have expired, (2) have been successfully challenged, (3) have been subject to a paragraph IV certification pursuant to which the patent owner or NDA holder has declined to sue within 45 days, (4) have been subject to a paragraph IV certification that led to a lawsuit and a 30-month stay that has since expired, or (5) are subject to a section viii statement and a corresponding labeling carve-out.

3. *ANDA Approval for a Drug Product Whose Labeling Omits an Indication that is Protected by a Patent*

Section 505(j)(2)(A)(i) of the Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." This language reflects Congress's intent that the generic drug be safe and effective for each "condition of use" prescribed, recommended, or suggested in the generic drug labeling. However, it does not require that an ANDA be approved for each condition of use for which the RLD is approved. In 21 CFR 314.92(a)(1), FDA has explicitly stated that a proposed generic drug product must have the same conditions of

[23] See also the final rule titled *Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed*, 68 FR 36676 (June 18, 2003). In the preamble to this final rule, we stated that the section viii statement permits an ANDA applicant to "avoid certifying to a patent by stating that it is not seeking approval for the use claimed in the listed patent" (68 FR 36676 at 36682). We stated, "[o]ur position has been that, for an ANDA applicant to file a section viii statement, it must 'carve-out' from the proposed ANDA labeling, the labeling protected by the listed patent" (id.).

use as the listed drug, except that "conditions of use for which approval cannot be granted because of . . . an existing *patent* may be omitted" (emphasis added).

The Act also requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug. . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the Act] or because the new drug and the listed drug are produced or distributed by different manufacturers" (section 505(j)(2)(A)(v) of the Act). A parallel provision appears in section 505(j)(4)(G) of the Act.[24]

Similarly, the regulations at 21 CFR 314.94(a)(8)(iv) require the following:

> Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the [generic] drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 [21 CFR 314.93] or because the drug product and the reference listed drug are produced or distributed by different manufacturers.

Section 314.94(a)(8)(iv) sets forth examples of permissible differences in labeling that may result because the generic drug product and reference listed drug are produced or distributed by different manufacturers. These differences include the following:

> . . .differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or *omission of an indication or other aspect of labeling protected by patent* [emphasis added] or accorded exclusivity under section 505(j)(4)(D) of the Act.[25]

The regulations at 21 CFR 314.127(a)(7) further provide that to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are *protected by patent* [emphasis added]," we must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."

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[24] Section 505(j)(4)(G) of the Act provides that FDA must approve an ANDA unless, among other things, "the information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for [the reference listed drug] except for changes required because of differences approved under [Section 505(j)(2)(C)] or because the drug and the listed drug are produced or distributed by different manufacturers."

[25] We note that due to a series of amendments to the Act, the reference in 21 CFR 314.94(a)(8)(iv) to section 505(j)(4)(D) of the Act corresponds to current section 505(j)(5)(F) of the Act.

Relevant case law affirms an ANDA applicant's ability to carve out protected labeling without violating the "same labeling" requirement. For example, in *Bristol Myers Squibb* v. *Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996), the D.C. Circuit ruled that "the statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for the use of the pioneer is a matter of indifference." Similarly, in *Sigma-Tau Pharmaceuticals, Inc.* v. *Schwetz*, 288 F.3d 141, 148, fn. 3 (4th Cir. 2002), the Fourth Circuit upheld the right of an ANDA applicant to carve out an indication protected by orphan drug exclusivity as a permissible difference due to a difference in the manufacturer.

Thus, under the statute, regulations, and applicable case law, the carve-out of patent-protected labeling is generally authorized as a permissible difference due to a difference in the manufacturer if the omission does not render the proposed drug product less safe or effective for the conditions of use that remain in the labeling.

II. ANALYSIS

In the Petition, you request that FDA

(1) publish a draft guidance on the demonstration of bioequivalence for locally acting oral inhalation suspension products,
(2) determine that labeling for a generic BIS product that omits once-daily dosing language would be legally impermissible,
(3) require any ANDA applicant for a BIS product to conduct a clinical trial program to demonstrate bioequivalence to Pulmicort Respules,
(4) consider whether it would be more appropriate to consider only applications submitted pursuant to section 505(b)(2) of the Act rather than ANDAs for approval of a generic BIS product, and
(5) require any generic BIS product to meet certain product quality standards.

For the reasons described in greater detail below, the Petition is denied in part and granted in part.

A. FDA Is Not Legally Required to Issue Guidance Prior to Approving ANDAs

You request that FDA publish a draft guidance on demonstrating bioequivalence for locally acting oral inhalation suspension products and allow a period of public comment on the guidance before approving any generic BIS products (Petition at 1). You acknowledge that FDA is not legally required to publish a guidance document prior to approving an ANDA for any generic BIS product, but you state that advance publication of such a guidance would facilitate

addressing the complexities of bioequivalence in this area (Petition at 1). In the September Supplement, you again assert that a guidance document should be made available for public review and comment before any ANDAs for any generic BIS product are approved (September Supplement at 3).

We deny your request. As you concede, neither the Act nor FDA regulations require FDA to issue a guidance prior to approving an ANDA. As in the new drug approval process, FDA is required to make decisions based on the information provided by individual applicants and to evaluate the scientific content of ANDAs to determine if the application meets the statutory and regulatory requirements (section 505(j) of the Act).

Although we are not legally required to issue a guidance prior to approving an ANDA, in May 2007, we issued our draft guidance for industry on *Bioequivalence Recommendations for Specific Products* in which we described FDA's process for making available to the public FDA guidance on how to design bioequivalence studies for specific drug products to support ANDAs.[26] We have been posting individual bioequivalence recommendations for specific drug products on our Web site,[27] and we have been announcing in a *Federal Register* notice the availability of the recommendations and the opportunity for the public to consider and comment on the recommendations. In the future, should we believe it would be appropriate to do so, we may issue a draft product-specific guidance on demonstrating bioequivalence for locally acting oral inhalation suspension products.

B. Omission of the Protected Aspects of the Generic BIS Labeling Is Legally Permissible and Does Not Render a Generic BIS Product Less Safe or Effective than the Listed Drug for All Remaining, Nonprotected Conditions of Use

You assert that the proposed IVAX label is legally impermissible because the omission of references to once-daily dosing and related safety and efficacy data would result in significant data gaps in the labeling (Petition at 4). You also assert that including the downward titration statement in the IVAX labeling would be legally impermissible because it would "teach" once-daily dosing (a protected method of use) but that omitting the downward titration statement also would be impermissible because important safety information would then be omitted from the labeling (Petition at 5). For the reasons described below, we disagree with your assertions.

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[26] FDA's draft guidance for industry on *Bioequivalence Recommendations for Specific Products* is available on our Web site at http://www.fda.gov/cder/guidance/index.htm.

[27] The draft product-specific bioequivalence recommendations are posted on our Web site at http://www.fda.gov/CDER/GUIDANCE/bioequivalence/default.htm.

1. The References to Once-Daily Dosing May Be Omitted from the Labeling

You state that in IVAX's notice letter pursuant to 505(j)(2)(B) of the Act regarding AstraZeneca's patents directed to once-daily dosing of nebulized budesonide, IVAX has informed AstraZeneca that it is proposing to eliminate references to once-daily dosing from the label of its proposed generic BIS (Petition at 4). You assert that the omitted material would necessarily include all of the safety and efficacy data related to once-daily dosing, which would leave significant data gaps in the labeled clinical information for the generic version of the drug product (Petition at 4). You also state that the lowest dosage strength in Pulmicort Respules is 0.25 mg once daily, and if IVAX's drug product were only labeled for administration twice a day, the lowest daily dose it would provide is 0.5 mg/day (0.25 mg administered twice a day) (September Supplement at 4-5 and October Supplement at 2). You state that "although the lowest effective dose will vary from patient to patient, as the Pulmicort Labeling clearly states, it has been established by clinical data that, for a significant patient population, the lowest effective dose of budesonide inhalation suspension is 0.25 mg once daily." (Petition at 4).

We disagree with your assertion that once-daily dosing may not be omitted from the generic BIS labeling without jeopardizing patient safety or effectiveness. As described in section I.C.3, the carve-out of patent-protected labeling is generally authorized, as you acknowledge, as a permissible difference in labeling due to a difference in the manufacturer if the omission does not render the proposed drug product less safe or effective than the listed drug for the non-protected conditions of use that remain in the labeling. Therefore, the issue is whether generic BIS, when labeled to exclude protected information currently in the Pulmicort Respules labeling, would be rendered less safe or effective than Pulmicort Respules for all remaining, nonprotected conditions of use. We have concluded that generic BIS, when labeled to exclude protected information on once-daily treatment of asthma with nebulized budesonide, would be as safe and effective as Pulmicort Respules for all remaining, nonprotected conditions of use.

The approved labeling for Pulmicort Respules includes in the DOSAGE AND ADMINISTRATION section a table with the recommended starting dose and highest recommended dose of budesonide based on prior asthma therapy. For patients previously on bronchodilator, inhaled corticosteroid, or oral corticosteroid therapy, the highest recommended dose of BIS is 0.5 mg total daily dose, 1.0 mg total daily dose, and 1.0 mg total daily dose, respectively. The Pulmicort Respules labeling stipulates that the recommended starting dose may be administered as either the total daily dose once daily or in divided doses twice daily. The Pulmicort Respules labeling also includes a statement below the dosing chart regarding consideration of an alternative once-daily dose for "symptomatic children not responding to non-steroidal therapy". The labeling also includes a statement stipulating that it is desirable to downward-titrate to the lowest effective dose once asthma stability has been achieved.

The generic BIS drug labeling would omit patent-protected references to once-daily dosing, such that the labeling would only include references to twice-daily dosing. Accordingly, for patients on previous therapy, the total recommended daily starting dose and highest recommended dose would be the same in the labeling for Pulmicort Respules and the generic BIS product.

A discussion of once-daily dosing versus twice-daily dosing is included in FDA's August 4, 2000, labeling review for the Pulmicort Respules NDA 20-929. The discussion is consistent with our conclusion that omission from the generic BIS labeling of patent-protected once-daily dosing would not render the generic BIS less safe or effective than Pulmicort Respules. The review states, in part, that

> "While the evidence supports the efficacy of the same nominal dose of Pulmicort Respules administered on either a once daily or twice daily schedule, the weight of the evidence by all measures is stronger for twice daily dosing."[28] The review also states, "In general 0.25 mg of Pulmicort Respules administered [twice daily] was numerically superior to 0.5 mg administered as a single daily dose (Four of four co-primary endpoints were significant in two clinical trials for 0.25 mg [twice daily] compared to one out of two in one clinical trial of 0.5 mg [once daily]; change from baseline in FEV_1 was significant in two of two trials for 0.25 mg [twice daily] compared to one of two for 0.5 mg [once daily]. A similar statement can be made for the comparison of 0.5 mg [twice daily] compared to 1.0 mg given as a single daily dose (Three of four co-primary endpoints were significant in two clinical trials for 0.50 mg [twice daily] compared to one of four in two clinical trials for 1.0 mg [once daily]). These data favor a [twice daily] schedule for dosing Pulmicort Respules over the same nominal dose administered once daily. In selecting a dosing schedule for Pulmicort Respules, it is important to take into consideration the mean treatment effect, as measured by controlled clinical trials, and the potential for the individual patient to respond better to an alternative dosing schedule. In particular, twice daily compared to once daily administration of the same nominal dose may be far more efficacious for an individual patient. It is noteworthy that published guidelines recommended downward titration of inhaled corticosteroids [to] the lowest dose effective in controlling a patient's symptoms. Accepted practice would therefore support testing a BID [twice-daily] dosing schedule of the same nominal dose before increasing the total daily dose to be administered once daily."[29]

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[28] A redacted version of the labeling review is available at http://www.fda.gov/cder/foi/nda/2000/20-929_Pulmicort%20Respules_Medr_P1.pdf. (See p. 3.)

[29] Id. at 3-4. (footnotes omitted).

The analysis in the review is also reflected in the CLINICAL TRIALS section of the approved labeling for Pulmicort Respules, which expressly states that "[t]he evidence supports the efficacy of the same nominal dose of [budesonide inhalation suspension] administered on either a once daily or twice daily schedule. However, when all measures are considered together, the evidence is stronger for twice daily dosing . . . ."[30] Because the weight of evidence is stronger in support of efficacy for twice-daily dosing as opposed to once-daily dosing (and safety has been demonstrated for both once-daily and twice-daily dosing), omission of once-daily dosing from the Dosage and Administration section chart (as well as from other sections) in the generic BIS labeling would not render the generic drug less safe or effective than Pulmicort Respules.

Likewise, omitting the following statement from the generic drug labeling would not render the generic drug less safe or effective than Pulmicort Respules: "In symptomatic children not responding to non-steroidal therapy, a starting dose of 0.25 mg once daily of PULMICORT RESPULES may also be considered." Because efficacy for a starting dose of 0.25 mg once daily was demonstrated in only one study and the evidence suggests that twice-daily dosing is more efficacious than once-daily dosing, the prior statement appears in the approved labeling (not as part of, but) below the recommended dosing table. The position of the statement below the dosing table reflects that the 0.25 mg once-daily dose "may also be considered" as an alternative for some patients, and this statement is in addition to the dosing recommendations in the table. Moreover, the above-mentioned downward titration statement that would also appear in the generic BIS labeling helps to ensure that patients receive the lowest effective dose, which, as you acknowledge, is highly variable from patient to patient.

Further, the type and incidence rate of adverse events corresponding to the 0.25 mg once-daily dose is not significantly different than that corresponding to the 0.5 mg and 1.0 mg total daily dose, and the adverse event table would retain references to the 0.5 mg and 1.0 mg total daily dose as well as the corresponding adverse events and incidence rates. As a result, physicians and healthcare providers would still be informed of the type and incidence of adverse events associated with generic BIS. Further, the generic drug labeling would retain important safety information in the warnings, precautions, contraindications, adverse events, and overdosage sections regarding, among others, systemic corticosteroid effects such as hypercorticism or growth suspension. Accordingly, we find that removing the statement regarding "consideration" of the alternative 0.25 mg once-daily dose from the labeling would not render the generic drug less safe or effective than Pulmicort Respules.

Our conclusion – that carving out once-daily dosing information from the generic BIS drug labeling (including the statement regarding consideration of an alternative once-daily dose)

[30] Because the generic drug would not bear both once-daily and twice-daily dosing information, this comparative statement would not be necessary and would be omitted from the generic BIS labeling.

would not render the generic drug less safe or effective than Pulmicort Respules – is consistent with our conclusions regarding AstraZeneca's other budesonide inhalation products, Pulmicort Flexhaler and Pulmicort Turbuhaler. Pulmicort Flexhaler was approved in 2006, well after the 1997 approval of Pulmicort Turbuhaler. The major difference between the two products is the addition of lactose to Pulmicort Flexhaler. Both products are inhalation-driven multidose dry powder inhalers approved for the maintenance treatment of asthma and as prophylactic therapy in adult and pediatric patients 6 years of age and older. The Pulmicort Turbuhaler labeling contains both once- and twice-daily dosing regimens (as well as an alternative once-daily dose that "may be considered"), whereas the Flexhaler labeling contains only the twice-daily dosing regimen. The product labeling for both products contains statements regarding downward titration to the lowest effective dose once asthma stability is achieved. FDA approved Pulmicort Flexhaler in 2006 as safe and effective without the once-daily regimen and the alternative once-daily dosing statement. The Pulmicort Flexhaler product containing the active ingredient budesonide was not considered either unsafe or ineffective without the once-daily dosing regimen and alternate once-daily dosing statement.

2. *It Is Appropriate To Include the Downward Titration Statement in the Labeling*

You state that the Pulmicort Respules labeling states, "In all patients, it is desirable to downward-titrate to the lowest effective dose once asthma stability is achieved" (Petition at 4). You state that Pulmicort Respules is proven effective when used once daily and although the lowest effective dose will vary from patient to patient, for a significant patient population, the lowest effective dose of BIS is 0.25 mg once daily (Petition at 4-5). You state that it would be impermissible for IVAX to include this downward titration statement in its product's label because the statement would "teach" once-daily dosing but the safety and effectiveness data that support once-daily dosing would not be in the label (Petition at 5). You state that it would also be impermissible for IVAX to omit this downward titration statement because important safety information would then be omitted from the label (Petition at 5). You assert that inclusion of the downward titration statement after elimination of the supporting clinical data would be legally improper because a company may not suggest a dosing regimen that is unsupported by data in the label, and inclusion of the downward titration statement would be misleading and render the drug misbranded (Petition at 5).

We disagree with your assertion that it would be impermissible to include or omit the downward titration statement from a generic BIS drug product's labeling. We find that it is appropriate to retain the downward titration of dosing statement in the generic BIS drug product's labeling. There are certain side effects associated with systemic exposure of corticosteroids, and, as you note in the September Supplement, it is important to minimize to the extent possible systemic exposure to these drugs (see September Supplement at 5). To minimize these risks, dosing

regimens, including doses other than to 0.25, 0.5, or 1.0 mg, or dosing frequencies alternative to twice-daily or once-daily dosing, may be chosen by a prescribing physician. As an example, alternate day dosing is a dosing frequency common to oral corticosteroids, although it is infrequently used with inhaled products. The downward titration statement is consistent with published guidelines for use of controller medications for asthma. For this reason, such statements are routinely a part of the labeling for intranasal and orally inhaled corticosteroid drug products (e.g., prednisolone sodium phosphate, triamcinolone acetonide), including the labeling for other orally inhaled budesonide products, Pulmicort Turbuhaler (once- and twice-daily dosing) and Pulmicort Flexhaler (only twice-daily dosing). It would therefore be appropriate to retain the downward titration of dosing statement in the generic BIS drug product's labeling.

We also find that inclusion of the titration statement in the labeling would not be misleading. The titration statement is relevant for the twice-daily dosing schedule that would be retained in the generic BIS product labeling. Titration to the lowest effective dose may involve, for example, a twice-daily regimen, once-daily dosing, or even alternate day dosing, as determined appropriate by a prescribing physician. The labeling does not state that the lowest effective dose is 0.25 mg once daily. As such, contrary to your assertion, the downward titration statement does not "teach" once-daily dosing.

Your statement in the Petition that for a "significant patient population" the "lowest effective dose is 0.25 mg once daily" is also incorrect (Petition at 4-5). The labeling does not state that the lowest effective dose is 0.25 mg once daily. Rather, the labeling states that "[i]n symptomatic children not responding to non-steroidal therapy, a starting dose of 0.25 mg once daily may also be considered." Because efficacy for a starting dose of 0.25 mg once daily was demonstrated in only one study and the evidence suggests that twice-daily dosing is more efficacious than once-daily dosing, the prior statement appears below the recommended dosing table. The position of the statement below the dosing table reflects that the 0.25 mg once-daily dose "may also be considered" as an alternative for some patients, and this statement is in addition to the dosing recommendations in the table. Further, physicians and healthcare providers are familiar with titration statements. Based on our experience and expertise, the lowest effective dose for BIS would not commonly be understood to be synonymous with a starting dose of 0.25 mg once daily that "may also be considered." Physicians and healthcare providers would understand from the titration statement that the lowest effective dose is highly variable and must by individualized for each patient. Therefore, as you acknowledge, "the lowest effective dose will vary from patient to patient" (Petition at 4), with some patients requiring higher doses or more frequent dosing and others needing lower than 0.25 mg once daily as the initial and/or maintenance dosing regimen. The downward titration statement does not specify or instruct that the dosing frequency must be once daily and need not be carved out as protected by the 6,598,603 and 6,899,099 patents.

Therefore, for the reasons described, we find that inclusion of the titration statement in the generic BIS labeling would be appropriate and would not be misleading. [31]

3. Your Other Assertions in the September Supplement Do Not Alter Our Conclusion

In the September Supplement, you assert that the situation involving Pulmicort Respules is different from that of Camptosar for which we determined that when information regarding the combination use of irinotecan with 5-fluorouracil and leucovorin is carved out from the labeling, generic irinotecan will remain safe and effective for the remaining, nonprotected conditions of use (September Supplement at 4).[32] In particular, you state that the labeling for a generic irinotecan hydrochloride product would be essentially the same as the labeling with which Camptosar was originally approved and marketed for four years, but when Pulmicort Respules was approved, its labeling provided for both once-a-day and twice-a-day administration for the same indication (September Supplement at 4). You also assert that based on recent data, more than 10% of prescriptions for Pulmicort Respules were written for a dose of 0.25 mg administered once per day and almost 30% of all prescriptions for 0.25 mg doses of Pulmicort Respules were written for once a day administration (September Supplement at 5). In addition, you assert that once-daily treatment with Pulmicort Respules results in better patient compliance than twice-daily treatment and improved patient compliance rates lead to more effective asthma control during long term treatment and may not require use of the product over as long a period of time (September Supplement at 5-6).

Your assertion that Pulmicort Respules is distinguishable from FDA's Camptosar decision because the labeling for Pulmicort Respules provided for both once-a-day and twice-a-day administration for the same indication when it was approved is not relevant. The fact alone that Pulmicort Respules provided for both once-a-day and twice-a-day dosing for the same indication when it was approved does not preclude us from concluding, as we have above, that omitting the once daily dosing from the generic BIS labeling would not render the generic BIS less safe or effective than Pulmicort Respules for the remaining, non-protected conditions of use.

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[31] In your October Supplement you also refer to several statements apparently made by IVAX in ongoing litigation involving two patents that relate to treating respiratory diseases, such as asthma, through administration by nebulization of a budesonide composition or suspension at a frequency of not more than once per day. IVAX's statements made during the course of patent litigation do not fetter FDA's discretion, as the agency with experience and expertise, to conclude that once daily patent-protected information may be carved out of the generic BIS labeling without rendering the generic drug less safe or effective than the innovator.

[32] Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Ernest Lengle, Ph.D., Executive Director, Regulatory Affairs, Watson Laboratories (July 28, 2008) (Docket No. 2008-P-0069).

In addition, your assertions regarding prescription practices and patient compliance are not relevant to whether twice daily dosing is safe and effective. As explained above, the evidence suggests that twice-daily dosing is more efficacious than once-daily dosing. In addition, the type and incidence rate of adverse events corresponding to the 0.25 mg once-daily dose is not significantly different than that corresponding to the 0.5 mg and 1.0 mg total daily dose and therefore physicians and healthcare providers would still be informed of the type and incidence of adverse events associated with the generic BIS drug product. Moreover, the generic BIS labeling would retain important safety information in the warnings, precautions, contraindications, adverse events, and overdosage sections. Accordingly, your assertions do not undermine our conclusion that a generic BIS drug product, when labeled to omit protected once-daily dosing information, would be as safe and effective as Pulmicort Respules for the remaining, nonprotected conditions of use.

C. ANDA Applicants May Demonstrate Bioequivalence of Their Generic BIS Drug Products to Pulmicort Respules Through In Vitro Tests

In the Petition, you assert that determining bioequivalence for BIS is more challenging for this inhalation suspension than for corticosteroid nasal sprays like Flonase (fluticasone propionate) (Petition at 7). You request that we require ANDA applicants to conduct a robust comparative in vitro and in vivo clinical program to demonstrate therapeutic equivalence of two BIS products (Petition at 13). For the reasons described in detail below, we deny your requests.

1. In Vitro Tests Are Appropriate to Demonstrate Bioequivalence Because of the Characteristics of BIS

You state that in a draft guidance and in a response to various citizen petitions concerning Flonase (fluticasone propionate), FDA has discussed what it considered an appropriate methodology for establishing bioequivalence for nonsystemic corticosteroid nasal sprays (Petition at 8). You concede that these documents apply only to nasal products and not pulmonary products, but you assert that the challenges FDA addressed are illustrative of difficulties that arise when attempting to assess bioequivalence in any locally acting suspension formulation (Petition at 8). You assert that although there are certain similarities between the nasal and pulmonary products, factors described in the petition (indication, long-term maintenance, symptom-based assessment, children versus adults, and suspension characteristics and product quality) make it more challenging to determine bioequivalence for this inhalation suspension than for corticosteroid nasal sprays like Flonase (fluticasone propionate) (Petition at 7, 10-12). You state that for Flonase we recommended, (1) qualitative and quantitative sameness of formulation of test and reference products, (2) comparability in container and closure systems, and in vitro and in vivo methods that demonstrate equivalent product performance (Petition at 8). You suggest that at a minimum a demonstration of bioequivalence of a generic BIS to Pulmicort

Respules should include a 12-week comparative clinical trial and a pharmacokinetic study to assess bioequivalence of systemic exposure as a surrogate for systemic long-term effects (Petition at 13-14).

We disagree with your assertion that the only way to demonstrate equivalence of two BIS products would be to conduct a robust comparative in vitro and in vivo clinical program. As you acknowledge the regulations authorize FDA to use "any other approach deemed adequate" to establish bioequivalence (Petition at 7). For the reasons described below, we have concluded that bioequivalence of a generic BIS product to Pulmicort Respules can be demonstrated by in vitro methods if an applicant is able to measure the particle size distribution. The ANDA applicant using this method would also be expected to demonstrate that the formulation of the proposed generic drug product is qualitatively and quantitatively the same as the reference product.

For locally acting products, as you point out, bioequivalence is generally not measured directly (Petition at 8). Because budesonide is a locally acting drug, the typical pharmacokinetic bioequivalence study that compares the rate and extent of absorption of the drug in the systemic circulation alone would not be sufficient to demonstrate equivalent delivery of budesonide to the lungs. As you also acknowledge, this type of study is less useful when used for products like budesonide that are not intended to be absorbed in the blood stream to elicit therapeutic effects (Petition at 7). In such cases, the Agency looks to alternative ways to determine whether significant differences in rate or extent of absorption exist between two products. We may rely on other methods to assess bioequivalence.[33] Taking into consideration the characteristics of BIS, we have concluded that in vitro methods are capable of assessing bioequivalence of budesonide under certain circumstances.

BIS is an inhalation suspension in which the active ingredient is undissolved and the inactive ingredients are dissolved in the suspending fluid. Suspension characteristics are important for oral inhalational products and are critical in determining whether in vitro methods alone are appropriate for determining bioequivalence for BIS. Because all the inactive ingredients in BIS are dissolved, if the inactive ingredients and active ingredient are qualitatively and quantitatively the same as the reference product, the only potential difference between the test and reference product would be the properties of the suspended drug substance (active ingredient) particles in the product. In a product that is qualitatively and quantitatively the same as Pulmicort Respules, there will be no other suspended particles to interfere with a determination of the particle size distribution of the BIS drug product. If there is equivalence in particle size between generic BIS and Pulmicort Respules, then the budesonide in generic BIS can be expected to be delivered at

[33] You also acknowledge that inhaled corticosteroids are one class of nonsystemic drugs for which FDA may establish alternative methods to show bioequivalence (Petition at 7).

the same rate and extent at the site of action (i.e., the lungs) as the budesonide in Pulmicort Respules. Assuming there is equivalence in particle size distribution, systemic availability would also be expected to be equivalent because the amount of budesonide absorbed into the blood stream after passing through the lungs would be expected to be equivalent. For these reasons, we believe that it is important to focus on the particle size of the active ingredient in evaluating generic BIS products.

We have identified the attributes of the particles that could potentially affect the availability of the delivered dose at the primary sites of action (i.e., in the lungs) and also the systemic availability of the delivered dose. These attributes include particle size distribution (in suspension and in the nebulized aerosol), polymorphic form of the particle, and drug particle size in the droplets.[34] We believe that through in vitro tests, ANDA applicants can demonstrate that there is no significant difference in these properties of the drug substance (active ingredient) particles and therefore no significant difference in both the local and the systemic availability of the generic and reference drug products.

For these reasons, based on our authority under section 505(j)(8)(C) of the Act and our regulations at 21 CFR 320.24(b)(6), we request that applicants for generic BIS demonstrate that their formulations are qualitatively and quantitatively the same as the reference product and conduct in vitro testing to demonstrate that they have particle size distributions equivalent to the reference product. The recommended in vitro equivalence tests are extensive and include the following:

- Unit dose content of drug in the ampules
- Mean nebulization time and mean delivered dose at the mouthpiece (% nominal dose) at the labeled flow rate of 5.5 liters/minute through such time that mist is no longer coming out of the mouthpiece.
- Particle size distribution of the active ingredient in the product and comparative particle size distribution in the suspension (in the ampule) and in the nebulized aerosol. The particle size distribution determination should be based on a validated method. Validation should demonstrate method sensitivity to drug particle size over the expected size range in the suspension. Drug particles and agglomerates in the suspension both in the ampule and the nebulized aerosol should be characterized for mean size and distribution.
- Sameness of polymorphic form based on X-ray diffraction

[34] See K.Dahlstrom, L.Thorsson, P.Larsson, and K.Nikander, "Systemic Availability and Lung Deposition of Budesonide via Three Different Nebulizers in Adults," Ann. Allergy Asthma Immunol., 2003;90: 226–232; W.K. Kraft, B.Steiger, D.Beussink, J.N.Quiring, N.Fitzgerald, H.E.Greenberg and S.A.Waldman, "The Pharmacokinetics of Nebulized Nanocrystal Budesonide Suspension in Healthy Volunteers," J. Clin. Pharmacol., 2004;44: 67-74.

- Sameness of shape (crystalline habit)
- Sameness of aqueous droplet size of the nebulized aerosol by a laser diffraction method[35]

If the applicant demonstrates bioequivalence through in vitro testing, we will not expect an ANDA applicant to conduct a clinical study to demonstrate bioequivalence.

Alternatively, if an applicant is unable to measure the particle size distribution, we will consider an applicant's proposal to perform the in vitro tests recommended above (with the exception of the test addressing particle size distribution) and also in vivo clinical and pharmacokinetic studies (in addition to demonstrating qualitative and quantitative sameness in formulation) to demonstrate bioequivalence. In vivo studies to establish bioequivalence would likely include (1) a clinical endpoint bioequivalence study for local delivery with demonstration of acceptable dose-response for test and reference products to assure study sensitivity and (2) a systemic exposure (pharmacokinetic) bioequivalence study. Prior to initiating such studies, applicants should submit a protocol with their proposal for both studies for our review.

You assert that determining bioequivalence for BIS is more challenging than for corticosteroid nasal sprays like Flonase. Although both Flonase and BIS are suspensions, BIS and Flonase have different characteristics that lead us to reasonably conclude that different methods may be appropriate for determining bioequivalence. Flonase consists of an aqueous suspension of microfine fluticasone propionate intended for topical administration to the nasal mucosa through a metered atomized spray pump and is classified as a nasal spray suspension. In contrast to BIS, both the active and inactive ingredients are undissolved in the Flonase suspension. In the case of Flonase, an analytical methodology was not available to determine the particle size distribution of the suspended drug substance (active ingredient) particles in the presence of undissolved inactive ingredient particles. In other words, at the time we provided bioequivalence recommendations for Flonase, it was not possible to assess particle size distribution of fluticasone propionate alone. Accordingly, a comparative in vivo bioequivalence study with a clinical endpoint to establish local delivery equivalence and a pharmacokinetic study to establish equivalent systemic exposure were considered appropriate to assess local and systemic absorption. As explained above, in contrast, only the active ingredient is undissolved and all inactive ingredients are dissolved in the BIS suspension and particle size distribution of budesonide can be measured using in vitro methods. Therefore, an in vitro testing method may be used to demonstrate bioequivalence of generic BIS drug products.

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[35] If an applicant is proposing both a 0.5 mg/2 ml and a 0.25 mg/2ml strength generic BIS drug product and if the micronized budesonide (bulk drug) used in the lower strength product is the same as that used in the higher strength product, i.e., same particle size, particle size distribution, polymorphic form, and shape, and the comparative test and reference lower strength formulations are qualitatively and quantitatively the same, then we recommend an abbreviated testing method for the lower strength BIS drug product.

Flonase and BIS are also distinguishable in the devices that are typically used with the drug products. Nasal suspension spray drug products, such as Flonase, include a spray device, and the performance of a nasal spray drug product is determined by the formulation (both active and inactive ingredients) and the spray device. Therefore, the bioequivalence methods for Flonase evaluated differences in both the device and formulation. Accordingly, a number of comparative in vitro studies were recommended for generic versions of Flonase, as described in FDA's draft guidance for industry on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action.*[36] In contrast, Pulmicort Respules is supplied in sealed aluminum foil envelopes and the nebulizer devices that are used with Pulmicort Respules are commercially available separately from the suspension product. Therefore, the bioequivalence evaluation for BIS drug products does not need to include an evaluation of the device. The generic BIS labeling, like the Pulmicort Respules labeling, would bear substantively the same instructions with respect to the device used to deliver budesonide. For example, the labeling would say that BIS "should be administered via jet nebulizer connected to an air compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask." To further ensure consistency between the size of droplets produced and the amount of drug delivered, we recommend that applicants for BIS conduct their bioequivalence testing using the same nebulizer described in the RLD labeling and used in the clinical trials for the RLD.

You also assert that certain factors described in the Petition (indication, long-term maintenance, symptom-based assessment, children versus adults, suspension characteristics and product quality) make it more challenging to determine bioequivalence for this inhalation suspension than for corticosteroid nasal sprays like Flonase (fluticasone propionate) (Petition at 7). Bioequivalence testing is intended to detect differences between product formulations. As discussed above, the characteristics of BIS and Flonase are different and lead us to conclude that in vitro methods (assuming assessment of particle size distribution) alone can be used to determine bioequivalence for generic BIS. Further, FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents; (3) they are bioequivalent; (4) they are adequately labeled; (5) they are manufactured incompliance with Current Good Manufacturing Practice regulations.[37] A generic BIS that is therapeutically equivalent to Pulmicort Respules can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.[38] We further discuss your proposed clinical program in the next section of this response.

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[36] FDA's draft guidance for industry on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (April 2003), available on our Web site at http://www.fda.gov/cder/guidance/index.htm.

[37] Orange Book at vii.

[38] Id.

In summary, based on the characteristics of BIS, ANDA applicants for BIS products that are qualitatively and quantitatively the same as Pulmicort Respules may demonstrate bioequivalence of their drug product to Pulmicort Respules by conducting in vitro tests if they can measure particle size distribution. FDA will also consider proposals involving a combination of in vitro and in vivo tests if an applicant is unable to measure the particle size distribution.

2. The Clinical Program Described in the Petition is Not Necessary To Demonstrate Bioequivalence

You assert that although there are certain similarities between the nasal and pulmonary products, factors described in the petition (indication, long-term maintenance, symptom-based assessment, children versus adults, and suspension characteristics and product quality) make it more challenging to determine bioequivalence for this inhalation suspension than for corticosteroid nasal sprays like Flonase (fluticasone propionate) (Petition at 7, 10). You assert that these factors must be accounted for in any clinical program designed to demonstrate therapeutic equivalence between a potential generic BIS and Pulmicort Respules (Petition at 13). You propose a clinical program that you assert would establish therapeutic equivalence (Petition at 13). You state that at a minimum, a program would consist of two trials: (1) an adequate, well-controlled 12-week clinical trial between test and reference products to provide reliable estimates for "equivalent effectiveness" and (2) a pharmacokinetic study to assess bioequivalence of systemic exposure as a surrogate for systemic long-term effects such as adrenal suppression, growth suppression, osteoporosis, etc. (Petition at 13-14). You describe in detail various study considerations regarding study design, statistical considerations, and the pharmacokinetic study for systemic exposure and safety equivalence (Petition at 14-17).

We do not believe that it would be appropriate to require all applicants for generic BIS drug products to conduct a comparative clinical study and pharmacokinetic study when they can use an in vitro method (assuming particle size distribution can be measured) to demonstrate bioequivalence. The in vitro method would obviate the need for human testing, and this approach is consistent with our desire to avoid unnecessary human testing. Under the recommended in vitro bioequivalence method, we would expect the total amount of drug nebulized, the particle size distribution of drug in the droplets, and the droplet size distribution to be bioequivalent between the generic BIS drug product and Pulmicort Respules. If the criteria are met, we can reasonably expect that there would not be a significant difference in the systemic exposure and local delivery between the two drug products because of the characteristics of the suspension in which the active ingredient remains undissolved.

We also believe that the in vitro bioequivalence method described above would be more sensitive to differences between two BIS products than the clinical trial that you propose. For example, you state that the selected doses must fall within the ascending portion of the dose-response

relationship and not in the flat portion, and that it is difficult to establish a dose-response relationship for inhaled corticosteroids in a mild population using standard outcomes, such as FEV_1,[39] as the dose-response relationship plateaus at relatively low doses (Petition at 14). You state that establishing the dose-response relationship is essential if bioequivalence is to be shown by a comparative clinical trial methodology (Petition at 14). We note that the apparent flatness of the dose-response relationship indicates that small changes in the amount of drug delivered are not easily detectable by clinical or pharmacodynamic measures. Therefore, the clinical study you propose likely would not be as sensitive to differences between two BIS products as would the in vitro bioequivalence method previously described.

In addition, as you state in the Petition, in children under 5 years of age, reproducible measures of lung function are claimed to be impossible, and variability in symptom scores are greater than variability in lung function testing (Petition at 15). You state that therefore a larger sample size is required to establish acceptable confidence limits for the estimated comparison between products (Petition at 15). Because Pulmicort Respules is indicated for the maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age, children under 5 years of age is a significant portion of the population for which the drug is indicated. We note that the variability in the proposed endpoint reduces the ability of the proposed clinical trial to detect differences between drug products. Again, we believe that a comparative clinical study such as the one you propose therefore likely would not be as sensitive to differences between two BIS drug products as would the in vitro bioequivalence method previously described.
As we described, applicants for generic BIS drug products who can measure particle size distribution may conduct in vitro tests to demonstrate bioequivalence. FDA will also consider applicants' proposals involving a combination of in vitro and in vivo tests if they are unable to measure particle size distribution and we intend to evaluate the appropriate endpoints when considering such proposals.

For the reasons described, we deny your request to require applicants for generic BIS to conduct your proposed clinical program to establish bioequivalence.

D. A 505(b)(2) Application Would Not Be Necessary Because BIS Can Be Approved as an ANDA

You suggest that the ANDA approval route is not appropriate for generic BIS because an extensive clinical program would be required to demonstrate bioequivalence for the generic drug product (Petition at 17-18). You assert that when extensive safety and efficacy trial data from well-controlled clinical trials are required to prove bioequivalence, it may be more appropriate to

[39] The FEV_1 is the Forced Expiratory Volume in 1 second, a pulmonary function test measuring the volume exhaled during the first second of a forced expiratory maneuver starting from the level of total lung capacity (i.e., after taking a maximal deep breath).

convert the application from an ANDA to an application submitted under section 505(b)(2) of the Act (Petition at 19).

In the September Supplement, you state that in FDA's briefing information for the July 23, 2008, meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, FDA stated that "no validated methods [for measuring potency] with acceptable sensitivity and precision are available" for inhaled corticosteroid products (September Supplement at 2). You assert that therefore FDA indicated that more information is needed about what types of studies may be relied upon to evaluate the bioequivalence of proposed generic versions of BIS drug products.

In the September Supplement, you also state that Dr. Paul Dorinsky of Teva Pharmaceuticals stated that no endpoint has been able to reproducibly be used to establish dose response for inhaled corticosteroids and proposed a three part clinical program for (1) a clinical pharmacology study for each dose to establish equivalence for the area under the plasma concentration versus time curve (AUC) and the maximum drug concentration (C_{max}), (2) a clinical efficacy study involving adults and adolescents of 12 weeks or longer using an established efficacy measure as the primary endpoint, with extrapolation of the results to children, and (3) a clinical safety study (or pharmacokinetic study) that evaluates the test and reference products to show comparable safety for children (September Supplement at 2). You assert that you do not agree that such studies are sufficient to measure the bioequivalence of inhaled corticosteroid drug products, but FDA's and Dr. Dorinsky's statements provide further evidence that generic BIS products should not be the subject of ANDAs (September Supplement at 2). You contend that both the type of studies proposed by Dr. Dorinsky, and those that you assert are required to measure bioequivalence of inhaled corticosteroids, are not considered to be limited confirmatory studies that can be submitted in support of an ANDA (September Supplement at 3).

We disagree with your assertion that an ANDA for a generic BIS should be converted to a 505(b)(2) application. As described in section II.C of this response, an applicant for a generic BIS drug product may demonstrate bioequivalence of its drug product to Pulmicort Respules through in vitro tests if the applicant is able to measure particle size distribution. If an applicant for a generic BIS drug product is unable to measure particle size distribution, we would consider the applicant's proposal to conduct a combination of in vitro and in vivo studies (in addition to demonstrating equivalence in formulation). For the in vivo studies, we would expect the applicant to perform (1) a clinical endpoint bioequivalence study for local delivery with demonstration of acceptable dose-response for test and reference products to assure study sensitivity and (2) a systemic exposure (pharmacokinetic) bioequivalence study. Whether the applicant conducts in vitro studies or a combination of in vitro and in vivo studies to assess bioequivalence, the application for the generic BIS drug product would be appropriate for submission as an ANDA.

The in vivo studies, as well as the in vitro studies, would be designed to evaluate the bioequivalence of the test and reference products and are appropriate for submission as an ANDA.[40] A clinical endpoint bioequivalence study would be submitted to demonstrate bioequivalence, rather than to demonstrate the safety and effectiveness of the generic BIS. As you acknowledge, FDA may review limited confirmatory studies as part of an ANDA and has used bioequivalence endpoints from clinical trials, as contemplated in the regulations, as the basis for approval of certain generic drug products (Petition at 19). In the preamble of the final rule of ANDA regulations, FDA stated "The fact that clinical trial data are submitted to demonstrate bioequivalence does not therefore force FDA to convert an application to a section 505(b) application."[41]

We also disagree with your assertion that FDA's and Dr. Dorinsky's statements provide further evidence that generic BIS drug products should not be the subject of ANDAs. As described in the *Federal Register* notice published on June 5, 2008 (73 FR 32030), the agenda for the meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology included a general discussion of the use of inhaled corticosteroid dose-response as a means to establish bioequivalence of inhalation drug products. The statements that you cite were made in the context of this general discussion about inhaled corticosteroids and not to specifically address what bioequivalence methodologies would be appropriate for generic BIS drug products.

We disagree with your conclusion that FDA's statement that "no validated methods [for measuring potency] with acceptable sensitivity and precision are available" indicates that more information is needed about what types of studies may be relied upon before FDA can evaluate the bioequivalence of proposed generic BIS drug products. Our reference to validated methods is in the context of a clinical endpoint or pharmacodynamic bioequivalence study for demonstrating local delivery of an inhaled corticosteroid generally. In the specific case of demonstrating bioequivalence for generic BIS drug products, as explained, based on the characteristics of BIS, we have determined that an in vitro study would be appropriate to demonstrate bioequivalence if an applicant can measure particle size distribution of its generic BIS drug product. If an applicant does not demonstrate the particle size distribution of its generic BIS drug product, we would consider applicants' proposals to conduct a combination of in vitro and in vivo studies as described previously, and we would consider proposals from applicants on the appropriate endpoints. When evaluating such proposals, we intend to consider the issue of a validated method for measuring potency in evaluating any applicant's proposal.

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[40] See 505(j)(2)(A)(iv) of the Act and 21 CFR 314.94(a)(7).

[41] 57 FR 17950, 17977-78 (April 28, 1992).

We therefore believe that submission of an ANDA is an appropriate regulatory pathway for seeking approval of a generic BIS drug product, and we deny your request.

E. BIS ANDAs Are Evaluated To Ensure That They Meet Product Quality Standards

You assert that generic drug products must be manufactured to the same quality standards as those for brand name drugs (Petition at 20). You state that the potential for inactive ingredients and other product quality markers to affect a product's safety and efficacy may be particularly pronounced in an inhalation suspension (Petition at 20-21). You assert that there are risks to patients if product quality for generic BIS is not meticulously assessed, and the generic version could be less or more potent than Pulmicort Respules or contain impurities, extractables, or leachables not found in Pulmicort Respules, which could contribute to asthma exacerbation (Petition at 21). You assert that the same the same product quality standards that AstraZeneca was expected to meet and address for Pulmicort Respules are just as important for generic BIS (Petition at 21-22). You state that an appropriate set of specifications for any generic BIS product would address, at least, the following characteristics (Petition at 22):

- Agglomerates
- Active pharmaceutical ingredient assay
- Appearance
- Color
- Content uniformity
- Disodium edetate assay
- Foreign particles
- Identity of API
- Impurities and degradation products
- Osmolarity
- Particle size distribution
- pH
- Potential leachables
- Sterility

In particular, you discuss the issues of (1) leachables and extractables, (2) impurities and degradation products, (3) sterility, (4) mass median diameter and particle size distribution, (5) agglomerates, and (6) container closure system (Petition at 22-25).

We agree that applicants for generic BIS products should address the characteristics that you have listed. Each of the specific attributes that you cite is included in the specification or the chemistry, manufacturing, and controls evaluation of generic BIS products, and we evaluate

ANDAs for generic BIS products to ensure the quality of the drug. We do not believe, however, a generic BIS applicant must have specifications that are identical to those contained in the NDA for Pulmicort Respules. As you acknowledge, manufacturing specifications applicable to the innovator and generic may differ due to different manufacturing processes or other variables (Petition at 20). FDA ensures when approving a generic BIS that the methods used in, or facilities and controls used for, the manufacture, processing, and packing of the drug are adequate to ensure the identity, strength, quality, and purity of the drug. With respect to the six issues that you discuss in particular, we address each issue in greater detail below and grant your requests to the extent described below.

1. Leachables and Extractables

You state that drug products packaged in semipermeable containers present particular difficulties regarding leachables and extractables (Petition at 22). In support of your Petition, you cite FDA's draft guidance on *Inhalation Drug Products Packaged in Semipermeable Container Closure Systems* (Petition at 22). You state that in accordance with this draft guidance, AstraZeneca has been required to test the plastics, foils, inks, and printing processes that are involved in the Pulmicort Respules container system and set stringent specifications for these, and also to investigate potential degradation or reaction products of impurities (Petition at 23). You state that FDA also specifically rejected any use of paper labeling or ink printing on semipermeable containers for Pulmicort Respules (Petition at 23). You state that given the importance of reducing impurities, particularly for this sensitive patient population, similar processes must be required for any generic version of BIS packaged in semipermeable containers (Petition at 23).

We agree that issues regarding the safety of extractable and leachable compounds should be evaluated for generic BIS products.[42] We expect generic BIS applicants to test the plastics, foils, inks, and printing processes that are involved in their container system. We do not recommend use of paper labeling or ink printing on semipermeable containers for generic BIS products. During our review of an ANDA for a generic BIS product, we will extensively evaluate the safety of the container closure system with respect to extractable and leachable compounds.

We disagree that applicants must follow similar testing processes as AstraZeneca for any generic BIS product in semipermeable containers. The container closure systems used by the ANDA

[42] *Extractables* are "compounds that can be extracted from elastomeric or plastic components of the container closure system when in the presence of a solvent," and *leachables* are "compounds that leach into the formulation from elastomeric or plastic components of the drug product container closure system." See FDA's guidance for industry on *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation* (July 2002), available on our Web site at http://www.fda.gov/cder/guidance/index.htm.

applicant may differ from those used by AstraZeneca for Pulmicort Respules. Therefore, the ANDA applicant's container closure systems may have different extractable or leachable compounds. Testing processes similar to that of the innovator may not be appropriate to ensure the safety of any particular container closure system.

2. Impurities and Degradation Products

You state that FDA required AstraZeneca to extensively test to determine what impurities and degradation products might be present in Pulmicort Respules and to toxicologically qualify any impurities and degradation products because this is a potential safety issue (Petition at 23). You state that FDA held AstraZeneca to higher standards than are recommended by International Conference on Harmonisation (ICH) guidance, particularly regarding potentially genotoxic impurities (Petition at 23). You state that for potentially genotoxic impurities or degradation products containing a structural alert, FDA requires specification levels of "not more than" 0.10% for AstraZeneca inhalation products, unless those impurities or degradation products have been toxicologically qualified (Petition at 23). You request that we require applicants for generic BIS products to apply similar testing standards and similar toxicological qualification processes to their drug products and, at a minimum, to test their products to determine what impurities or degradants may exist and characterize any existing impurities or degradants (Petition at 23).

We agree that applicants should test their drug product to determine what impurities or degradants may exist and should either demonstrate that the drug product meets the applicable qualification threshold for the genotoxic or structural alert impurity or qualify the impurity. We expect applicants for ANDAs, like those for NDAs, to adhere to testing standards and toxicological qualification processes for genotoxic and structural alert impurities that are applicable at the time their applications are being evaluated.

At the time Pulmicort Respules was approved, the ICH guidelines were silent on the issue of genotoxic impurities or impurities with a structural alert. In 2003, when AstraZeneca's chemistry supplement was being evaluated, the qualification threshold for each impurity in the drug product was 1% for a daily drug dose of less than 10 mg based on the 1997 guidance for industry on *ICH Q3B Impurities in New Drug Products*, which stated that the qualification threshold for an impurity for a daily dose < 10 mg was 1% or 50 micrograms (mcg), whichever was lower. For genotoxic impurities or impurities with a structural alert, the guidance did not provide a qualification threshold; therefore, a safety factor of 10 was added to allow such impurities to be present in the drug product without additional toxicological qualification at a level of less than 0.1% for a daily drug dose less than 10 mg. Accordingly, we expected AstraZeneca to limit the level of each genotoxic and structure alert impurity present in Pulmicort Respules to less than 0.10%.

Since that time, FDA has continued to evaluate the issue of genotoxic impurities. Based on our evaluation of the scientific information currently available and current international standards for potentially genotoxic impurities,[43] FDA is requesting that potentially genotoxic impurities in NDAs and ANDAs be limited to below a threshold of toxicological concern (TTC) of 1.5 mcg/day. For a chronically administered drug (>12 months) such as a generic BIS drug product, the maximum allowable daily dose for each genotoxic and structural alert impurity would be 1.5 mcg unless the impurity has been toxicologically qualified.[44] We are expecting ANDA applicants for generic BIS drug products to comply with this standard.

3. Sterility

You state that AstraZeneca extensively examined both the sterilization process used and the potential impurities or degradation products that may result from use of heat sterilization and request that we require the same of ANDA applicants (Petition at 24).

We grant your request in part. We expect ANDA applicants for generic BIS to demonstrate that they have sterile manufacturing processes and meet appropriate United States Pharmacopeial (USP) tests for sterility of the final product. ANDA sponsors are expected to identify and set appropriate limits on all potential degradation products. We encourage ANDA applicants to identify the origin of degradation products and use this information in the design of their manufacturing processes. However, we do not require ANDA applicants to identify the origin of particular degradation products as resulting from the use of heat sterilization because the safety of the drug product is determined by the levels of degradation products that are actually present and not by the origin of these degradation products.

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[43] EMEA (European Medicines Agency), 2006; D.Jacobson-Kram and T.McGovern, "Toxicological overview of Impurities in Pharmaceutical Products," Adv. Drug Deliv. Rev., 2007;59: 38-42; T.McGovern & D.Jacobson-Kram, "Regulation of Genotoxic and Carcinogenic Impurities in Drug Substances and Products," TrAC Trends in Analytical Chemistry, 2006;25: 790-795. We note that the international scientific community has been actively discussing what is an acceptable level for any genotoxic impurity for many years now, and a standard for genotoxic impurities in general is being established. The EMEA first issued a draft guideline in 2004 that recommended an acceptable level for NMT 1.5 mcg/day total daily intake based upon the FDA's threshold of toxicological concern that was published in the *Federal Register* regarding food contact materials, and the EMEA *Guideline on the Limits of Genotoxic Impurities* was finalized in June 2006 and came into effect on January 1, 2007. See also EMEA, Question & Answer on the CHMP Guideline on the Limits of Genotoxic Impurities, Revision 1, June 26, 2008.

[44] As stated previously, at the time AstraZeneca's supplemental NDA for Pulmicort Respules was evaluated, the qualification threshold for each genotoxic and nongenotoxic impurity in the drug product was 0.1 and 1%, respectively, for a daily drug dose of less than 10 mg. However, the percentage for qualification of each genotoxic and structural alert impurity is no longer being used. Presently, the threshold of toxicological concern of 1.5 mcg/day is applied to each genotoxic and structural alert impurity, regardless of concentration.

4. Mass Median Diameter and Particle Size Distribution

You state that the particle size distribution in suspension formulations has the potential to influence the rate of dissolution and the extent of drug availability at the sites of action in the lungs and to the systemic circulation (Petition at 24). You also state that AstraZeneca has been held to tight specifications for this parameter (Petition at 24). You request that we require that applicants demonstrate a tight control of the particle size distribution specification to ascertain consistent efficacy and safety within various batches of the same product as well as comparable efficacy and safety between a test product and the RLD (Petition at 24).

We grant your request in part. As described in section II.C of this response, ANDA applicants for generic BIS drug products can demonstrate bioequivalence using in vitro methods if they demonstrate that they have particle size distributions equivalent to the RLD. Each batch of the generic BIS drug product is subject to a particle size specification, and we expect applicants to demonstrate a tight control over the particle size distribution.

We do not intend to require an ANDA specification to include a limit on the mass median diameter. The mass median diameter is derived from the particle size distribution. Because we are expecting ANDA applicants to demonstrate that they have particle size distributions equivalent to the RLD, the specification regarding the particle size distribution is sufficient to ensure acceptable values of the mass median diameter.

5. Agglomerates

You state that the presence and extent of agglomerates may be important for the availability of the drug, in other words, that the presence of agglomerates may influence the amount and distribution of the drug in the nebulized droplets of different sizes, and may have consequences on efficacy and safety (Petition at 24). You state that AstraZeneca has been required to conduct extensive characterization and enumeration testing to support the finished drug product specification, and you request that we require the same of ANDA applicants (Petition at 24).

We grant your request in part. Agglomerate characterization is included in the release specification for all generic BIS drug products, and we request that ANDA applicants provide an appropriate method of characterizing agglomerates in their drug products. The ANDA applicant is expected to demonstrate that the method is an appropriate, scientific method to evaluate product quality. We do not require that the method used by the ANDA applicant be identical to the method used by AstraZeneca because differing methods may be scientifically appropriate for characterizing agglomerates.

6. Container Closure

You state that the shape and volume of the primary container may potentially have an impact on the drug product stability profile under various storage and transportation conditions (Petition at 24). You state that AstraZeneca has been required to thoroughly investigate and optimize the primary container design, ensuring that the dispensed dose from each Pulmicort Respules ampule falls within certain specifications, even when subjected to transportation simulation studies (Petition at 24). You request that we require applicants to assess the transportation effect on the product, particularly as related to the container closure system (Petition at 24). You assert that you have examined the IVAX container closure system available in Italy and that the ampule of the product is not optimized with regard to shape and volume resulting in negative effects on the IVAX product drug stability profile (Petition at 24). You assert that you conducted a transport simulation study on the IVAX product and observed a resulting decrease of about 20 percent in dispensed dose (Petition at 24). You state that if IVAX intends to use the same container in the United States, IVAX should assess and FDA should review this container closure issue prior to product approval (Petition at 25).

To the extent you request that ANDA applicants evaluate transportation effects on product stability, we grant your request. We have requested that ANDA applicants evaluate transportation effects on the stability of their proposed drug product and submit the results of their studies. We will evaluate these results to ensure that the proposed product exhibits an appropriate drug stability profile.

Therefore, for the reasons and to the extent described above, we grant in part your requests regarding product quality standards.

III. CONCLUSION

For the reasons described in this response, the Petition is granted in part and denied in part.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research